AMENDMENTS TO THE SPECIFICATION

Please replace paragraph [0004] with the following amended paragraph [0004]:

[0004] Natural killer (NK) cells have been found to specifically interact with a C-terminal localized epitope of Hsp70 (Botzler et. al. (1998) Cell Stress & Chaperones, 3, 6), that is presented on the cell membrane of tumor cells (Multhoff et. al. (1995) Int. J. Cancer, 61, 272; Multhoff et. al. (1997) J. Immunol. 158, 4341). The amount of membrane-bound Hsp70 on tumor cells positively correlates with the sensitivity to the lysis mediated by NK cells: Physical (heat) as well as chemical (cytostatic drugs) stress has been found to increase Hsp70 cell surface expression on tumor cells and thereby rendering them better targets for NK cells (Multhoff (1997) Int. J. Hyperthermia 13, 39; Botzler et. al. (1999) Exp. Hematol. 27, 470; Rabinovich et. al. (2000) J. Immunol. 165, 2390; Feng et. al. (2001) Blood 97, 3505). Incubation of purified NK cells with recombinant Hsp70-protein increases their cytolytic activity against Hsp70 membrane-positive tumor cells (Multhoff et. al. (1999) Exp. Hematology 27, 1627). The same effect is achieved by a 14 amino acid peptide, termed TKD (TKDNNLLGRFELSG (SEQ ID NO:1), aa450-463), derived from the C-terminal domain of Hsp70. This region corresponds to the domain of Hsp70 exposed to the extracellular milieu of viable tumor cells (Multhoff et. al. (2001) Cell Stress & Chaperones 6, 337). Concomitant with an increased cytolytic activity, following contact either with Hsp70-protein or with Hsp70-peptide TKD the cell surface expression of the activating form of the C-type lectin receptor CD94 was enhanced in NK cells. Blocking assays using an inhibitory antibody specific for CD94 revealed an involvement of CD94 in the interaction of NK cells with Hsp70 membrane-positive tumor cells (Multhoff et. al. (1999) Exp. Hematology 27, 1627). These data indicate that apart from HLA-E presenting leader peptides of classical HLA-alleles (Lanier et. al. (1998) Immunity 8, 693; Braud et. al. (1998) Nature 391, 795), the C-terminal localized Hsp70-peptide sequence TKD might be considered as a potential ligand for a yet undefined activating CD94 receptor complex. Although the preceding observations indicate that Hsp70-peptide functions as a tumor-selective target recognition structure for CD94 positive NK cells (Multhoff et al. (1997) J. Immunol. 158, 4341), the mechanism by which NK cells lyse Hsp70 positive tumor target cells remained to be elucidated. In addition, it is desirable to specifically trigger the lytic activity of NK cells towards tumor cells in a more specific manner than has hitherto been possible. All these

scientific goals serve as a means to derive more efficacious and more specific approaches to disease treatment and in particular to tumor treatment.

Please replace paragraphs [0008] through [0012] with the following amended paragraphs[0008] through [0012]:

[0008] Accordingly,.the present invention relates to a method of inducing or enhancing the expression of granzyme B in natural killer (NK) cells comprising contacting NK cells with [0009] (a) Hsp70 protein; [0010] (b) a (C-terminal) fragment of (a) comprising the amino acid sequence TKDNNLLGRFELSG (SEQ ID NO:1); [0011] (c) a (poly)peptide comprising the amino acid sequence TKDNNLLGRFELSG (SEQ ID NO:1); or [0012] (d) a combination of (a), (b) and/or (c).

Please replace paragraph [0030] with the following amended paragraph [0030]:

[0030] Methods for the stimulation of NK cells by incubation with Hsp70 proteins of C-terminal fragments thereof have been described in WO 99 49 881. Surprisingly it has been found, that expression of granzyme B is induced or enhanced in NK cells by contacting said cells with Hsp70 protein, a fragment thereof comprising the amino acid sequence TKDNNLLGRFELSG (SEQ ID NO:1), a (poly)peptide comprising the amino acid sequence TKDNNLLGRFELSG (SEQ ID NO:1), or a combination of said proteins/(poly)peptides preferably in combination with IL-2. Preferably, the fragment referred to above and in connection with other (preferred) embodiments of the invention is a carboxy-terminal (C-terminal) fragment of Hsp70.

Please replace paragraph [0032] with the following amended paragraph [0032]:

[0032] According to the invention, the term "fragment" of the Hsp70 protein also comprises (poly)peptides exhibiting an amino acid sequence from the range of amino acids 384-641 of the human Hsp70. All C-terminal (carboxy-terminal) fragments at least comprise the amino acid sequence TKDNNLLGRFELSG (SEQ ID NO:1). Methods for the isolation of corresponding (poly)peptides are known in the art and particularly described in the appended example 1. Thus, the person skilled in the art is also able to produce fragments from the above-mentioned fragment 384-641 by recombinant techniques without further ado (standard methods for this are

described in Sambrook et al., "Molecular Cloning, A Laboratory Manual", 2. edition 1989, CSH Press, Cold Spring Harbor, N.Y.) and test them for the activation properties wanted.

Please replace paragraphs [0034] through [0035] with the following amended paragraphs[0034] through [0035]:

[0034] In one alternative (poly)peptides comprising the amino acid sequence TKDNNLLGRFELSG (SEQ ID NO:1) are (poly)peptides consisting of the recited amino acid sequence and optionally further amino acid stretches N-terminally and C-terminally thereof derived from Hsp70, fused to further randomly chosen or naturally occuring amino acid sequences. Thus, the method of the present invention relates to the stimulation of NK cells by fusion proteins comprising the sequence of the 14-mer Hsp70-peptide.

[0035] A preferred embodiment of the invention relates to a method wherein the Hsp70 protein, the (C-terminal) fragment thereof, the (poly)peptide comprising the amino acid sequence TKDNNLLGRFELSG (SEQ ID NO:1), or the combination thereof is in an uncomplexed state.

Please replace paragraph [0037] with the following amended paragraph [0037]:

[0037] Thus, according to the methods described in WO 99 49 881 the person skilled in the art is able stimulate NK cells using Hsp70 protein or (poly)peptide comprising the amino acid sequence TKDNNLLGRFELSG (SEQ ID NO:1) in an uncomplexed state.

Please replace paragraph [0041] with the following amended paragraph [0041]:

[0041] This method comprises isolation of NK cells or a population of cells comprising NK cells as described herein above, wherein a physiological cell suspension containing NK cells is mixed with Hsp70 protein, the C-terminal fragment thereof or a derivative thereof or a protein/(poly)peptide comprising the amino acid sequence TKDNNLLGRFELSG (SEQ ID NO:1) and incubated to induce or enhance expression of granzyme B in the NK cells.

Please replace paragraph [0046] with the following amended paragraph [0046]:

[0046] In another preferred embodiment of the method of the invention said contacting of the NK cells with Hsp70 protein, the (C-terminal) fragment thereof or a derivative thereof or a protein/(poly)peptide comprising the amino acid sequence TKDNNLLGRFELSG (SEQ ID

NO:1) is effected for at least 12 hours. According to a further preferred embodiment said contacting is effected for at least 4 days.

Please replace paragraphs [0049] through [0053] with the following amended paragraphs [0049] through [0053]:

[0049] An alternative embodiment of the invention relates to the use of NK cells which produce (i.e. express) granzyme B after stimulation with [0050] (a) Hsp70 protein; [0051] (b) a (C-terminal) fragment of (a) comprising the amino acid sequence TKDNNLLGRFELSG (SEQ ID NO:1); [0052] (c) a (poly)peptide comprising the amino acid sequence TKDNNLLGRFELSG (SEQ ID NO:1); or [0053] (d) a combination of (a), (b) and/or (c); for the preparation of a pharmaceutical composition for the treatment of tumors, viral and bacterial infections and inflammatory diseases.

Please replace paragraph [0056] with the following amended paragraph [0056]:

[0056] Examples of suitable pharmaceutically acceptable (tolerable) carriers are known to the person skilled in the art and comprise, for example, phosphate-buffered saline solutions, water, emulsions, such as oil/water emulsions, sterile solutions, and so on. The pharmaceutical compositions (pharmaceutical preparations) containing such carriers may be prepared according to common methods. The pharmaceutical compositions may be administered to the respective individuals in an appropriate dosage. Ways of administration are, for example, intravenous (i.v.), intraperitoneal (i.p.), intratumoral, subcutaneous (s.c.), intramuscular (i.m.), topic or intradermal. The dosage depends on many factors, e.g. on the patient's size, sex, weight, age as well as the type of the composition specially administered, the kind of administration and so on. The compositions may be administered locally or systemically. Generally, administration is carried out parenterally. Therefore, the NK cells treated with Hsp70 protein, the C-terminal fragment thereof or a derivative thereof or a protein/(poly)peptide comprising the amino acid sequence TKDNNLLGRFELSG (SEQ ID NO:1) according to the invention are preferably injected intravenously. An injection may also be carried out directly into the tumour with an effective amount of NK cells being injected. Other known types of application are, of course, also possible. An operable number of NK cells administered includes the range of $5x10^7$ to $2x10^9$ NK cells, for example, as components of a leukapheresate. In such a leukapheresate, NK

cells are usually present in an amount of between 5% and 20%.

Please replace paragraph [0082] with the following amended paragraph [0082]:

[0082] FIG. 1B: The tryptic peptides (SEQ ID NOS:2-6) of the Coomassie-blue stained 32 kDa band of fraction 3 (F3), derived from the TKD column, correspond to human granzyme B. The probability of identification was 100% and the estimated Z-score was 1.89 corresponding to >95% confidence.

Please replace paragraph [0102] with the following amended paragraph [0102]:

[0102] Bovine serum albumine (BSA, 1 mg/ml, Sigma-Aldrich, Steinheim, Germany), 1 mg/ml lyophylized, recombinant human Hsp70-protein (Stressgen, British Columbia, Canada) or 2 mg/ml Hsp70-peptide TKD (TKDNNLLGRFELSG (SEQ ID NO:1), $aa_{450-463}$, Bachem, Bubendorf, Switzerland) were incubated with equilibrated AminoLink agarose beads (Pierce, Rockford, USA) in 2 ml for 6 h, together with the reductant $NaCNBH_3$. Binding capacity of BSA, Hsp70-protein and Hsp70-peptide TKD was greater 95%. Following removal of uncoupled material by extensive washing with Tris-buffer and quenching of non-reactive groups, cell lysates were administered to the BSA, Hsp70-protein and Hsp70-peptide TKD conjugated columns for 1 h.